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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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THE NATH LAW GROUP
112 South West Street
Alexandria, VA 22314

EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	
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06/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/617,350	NAMBURI ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-13,15-20 and 22-42* is/are pending in the application.

4a) Of the above claim(s) *9-13 and 24-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 15-20, 22-23, and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-7, 9-13, 15-20, 22-42 are presented for examination

Applicants' response and amendments to the claims, filed 4/1/2009, are acknowledged and entered.

Claims 9-13 and 24-41 remain withdrawn from consideration. Claims 1-7, 15-20, 22-23, and 42 are presently under examination.

Applicants' arguments, filed 4/1/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/1/2009 has been entered.

Claim Rejections - 35 USC § 102/103 – New Ground of Rejection

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 23 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over **Gilis *et al.*** (WO 00/03697; Published Jan. 27, 2000).

Instant claim 23 recites a pharmaceutically acceptable particle produced by the process of claim 1.

Applicant's attention is directed to MPEP 2113, which discusses the patentability of product-by-process claims. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Gilis *et al.* teach pharmaceutically acceptable particles comprising a water-insoluble azole antifungal agent and a water-soluble polymer coated onto core particles (page 14, lines 6-12; Example at pages 14-16; claims 1-6). Gilis *et al.* teach residual dichloromethane content of less than 600 ppm, preferably less than 250 ppm, which reasonably meets the limitation "..said oral dosage form is essentially free of methylene chloride" (page 4, lines 24-32; claims 1-6).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 15-16, 18-20, 22-23, and 42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Gilis *et al.*** (WO 00/03697; Published Jan. 27, 2000) and **Ishibashi *et al.*** (U.S. Patent Application Publication No. US 2003/0012815 A1; Published Jan. 16, 2003; Filed Jan. 26, 2001) in view of **Lynenskjold *et al.*** (US 2003/0211168 A1; Published Nov. 13, 2003; Filed Feb. 19, 2001) and **Nara *et al.*** (USP No. 6,245,351 B1; Issued Jun. 12, 2001; Filed Mar. 4, 1997), each already of record, for the reasons set forth at pages 8-12 of the previous Office Action dated 12/4/2008, of which said reasons are herein incorporated by reference.

No claim amendments have been made subsequent to the Office Action dated 12/4/2008. The claims recite a method of manufacturing a water-insoluble azole antifungal agent oral dosage form comprising the steps of:

1) providing a single phase working solution comprising a) a water-insoluble azole antifungal agent; b) water; c) a water-soluble polymer, and d) a solvent selected from the group consisting of alcohol, acetone, and mixtures thereof;
2) providing core particles formed from a pharmaceutically acceptable material;
3) combining said working solution with said particles to produce water-insoluble azole antifungal agent-coated particles;
4) drying said water-insoluble azole antifungal agent-coated particles; and
5) forming said dried particles into an oral dosage form,

wherein said working solution is essentially free of methylene chloride, and said oral dosage form is essentially free of methylene chloride.

Gilis et al. teach pellets having a core coated with an antifungal and a polymer (Abstract). With respect to solvents used in forming coated core particles, the reference discloses that dichloromethane and methanol are both Class 2 solvents whose presence in pharmaceutical products should be limited (page 2, lines 28-30). Specifically, the pellets disclosed in Gilis *et al.* comprise: a) a central, rounded or spherical core having a diameter of about 710-1190 μM); b) a coating film of a **water-soluble polymer** and an **antifungal agent**; and c) a seal-coating polymer layer, characterized in that the residual solvent levels in said pellets is within limits set by the ICH, that is, the concentration of dichloromethane is less than 600 ppm, most preferably less

than 250 ppm (page 4, lines 24-32). Accordingly, Gilis *et al.* disclose using ethanol as an alcoholic co-solvent that is necessary for applying the drug coat layer to the cores (page 4, lines 34-35), thus meeting the limitations of claim 15. Water-soluble polymers include those recited in instant claim 16, for example, hydroxypropyl methylcellulose, polyvinylpyrrolidones and methacrylates (page 6, line 23 to page 7, line 3). Such polymers are disclosed to have an apparent viscosity of 1 to 100 mPas when dissolved in a 2% aqueous solution, thus reasonably encompassing the limitations of instant claim 4 (page 5, lines 32-34). With respect to the composition of the core particles recited in instant claims 18-19, Gilis *et al.* disclose identical core particles composed of, for example, mannitol or microcrystalline cellulose (page 5, lines 8-19). Preferred antifungal agents for use as drugs in the drug-coating layer are lipophilic azole antifungals, in particular itraconazole (page 7, lines 10-11). The instantly claimed weight ratio of active agent to polymer is obviated by those disclosed at page 7, lines 15-30, for example, 1:1 to 1:5. With respect to the limitations of instant claim 22 wherein an external coating is applied to the drug coated spheres, Gilis *et al.* disclose such an external coating at page 8, lines 28-32. The addition of surfactants as recited in instant claim 3 is disclosed at page 9, lines 1-4. A drying step as recited in claim 1 is disclosed at page 10, lines 32-38).

The reference thus clearly suggests a process of forming drug-coated particles comprising the same steps as those instantly claimed. For example, at page 9, lines 14 to page 11, line 27, Gilis et al. describes a method of preparing coated pellets comprising the steps of: 1) preparing a drug coating solution by dissolving into a "suitable solvent system" appropriate amounts of an antifungal agent and a water-soluble polymer, wherein the solvent system comprises a mixture of methylene chloride and an alcohol, preferably ethanol; 2) providing core particles formed from a pharmaceutically acceptable material; 3) combining said drug coating solution with said particles to produce antifungal agent-coated particles; 4) drying said antifungal agent-coated particles; and 5) forming said dried particles into an oral dosage form. Further, Gilis *et al.* suggest that the dichloromethane content of the coating should be limited, such as by drying in a microwave. Gilis *et al.* differ from the claims **only** with respect to the solvent used in the coating solution. Whereas Gilis et al. used a solvent comprising a water-soluble polymer, methylene chloride, and an alcohol, the instant claims recite a solvent comprising a water-soluble polymer, water, and alcohol, acetone, or mixtures thereof.

However, Ishibashi *et al.* disclose drug-containing core substances having a multi-layered coating layer (Abstract). With respect to the coating solution used to coat the disclosed core particles, the reference discloses that the solvent system should dissolve both the hydrophobic organic compound and water-soluble polymer (page 6, ¶ [0057]). Suitable solvents include alcohols such as ethanol as well as ketones such as acetone (*id.*). The reference thus teaches that ethanol and acetone are suitable solvents for applying a coating solution to a core particle. The reference does not teach coating solutions additionally comprising water as instantly claimed.

However, Lynenskjold *et al.* teach a process for the production of drug carrier pellets comprising spray-drying a solution of a physiologically tolerable cellulosic binder containing an active drug (Abstract; Example 5). With respect to active drug substances coated onto the spray-dried pellets, the inventors teach that the antifungal, ketoconazole, as recited in claim 42, is one such active drug substance (page 4, [0046]). The active drug substance will generally be applied to the spray-dried pellets in the form of a solution or dispersion in a physiologically tolerable solvent or solvent mixture, optionally incorporating other components such as binders, sweeteners, pH modifiers, antioxidants, etc. (page 4, [0050]). The coatings may also include further components, including antiadhesives, which are reasonably interpreted as surfactants as recited in claims 3 and 17 (page 5, [0057]). With respect to the coating solutions, while the use of aqueous solutions or dispersions is preferred, organic solvents such as ethanol and acetone as recited in the instant claims may also be used (page 5, [0058]). Methylene chloride, as taught in Gilis *et al.* cited *supra*, may be used but is generally not preferred (*id.*).

Similarly, Nara *et al.* teach solvents for coating solutions may be water, an organic solvent, or mixtures thereof (col. 6, lines 34-35). The organic solvent may be any organic solvent capable of dissolving a water-insoluble substance, such as ethanol or acetone as recited in the instant claims (col. 6, lines 38-46). Water and its mixture with an organic solvent are "preferably used as solvent of coating composition" (col. 6, lines 47-48).

The above cited references continue to render the instant claims obvious because optimization of coating solutions for applying drugs to core particles is clearly a matter of routinely testing different solvent mixtures for optimal dissolution of active agent. The fact that Applicants use water instead of methylene chloride as disclosed in Gilis *et al.* does not render in the instant claims patentable in view of the fact that Ishibashi, Lynenskjold, and Nara all disclose

the use of solvents not containing methylene chloride for coating core particles, and Gilis et al. explicitly teaches that the methylene chloride content of the coated particles should be minimized. As such, one skilled in the art would immediately see the benefit of using a coating solution that omits methylene chloride, such as a coating solution comprising water, a water-soluble polymer, and a solvent selected from an alcohol, acetone, and mixtures thereof as motivated by the cited prior art.

Response to Applicant's Arguments

Applicants traverse the instant rejection, stating that the cited references do not establish a prima facie case of obviousness against the presently pending claims. The Examiner recognizes that in order to establish a prima facie case of obviousness, the Office must determine whether the improvement is more than the predictable use of prior art elements according to their established functions; whether the proposed modification of the prior art has a reasonable expectation of success; and whether the prior art references teach or suggest all the limitations of the claims.

Applicants argue that the Examiner has not met his burden of establishing a prima facie case of obviousness. In support of this argument, Applicants allege that the combination of references do not show all the elements of the pending claims in one working solution. Applicant's argument that Gilis et al. and Ishibashi et al. both disclose dichloromethane as a suitable solvent, in contrast to the claimed working solution, is unimpressive because it is directed to the individual teachings of the references without considering the references as combined with Lynenskjold and Nara, who both suggest the use of water-containing coating solutions for coating particles, including mixtures of water with an organic solvent such as ethanol or acetone. Furthermore, Ishibishi teaches that ethanol and acetone are suitable solvents for applying a coating solution to a core particle, and Gilis et al. discloses that dichloromethane levels should be limited. Gilis et al. accomplish the limitation of dichloromethane levels by drying the coated particles *after* applying the coating solution. Applicants accomplish the limitation of dichloromethane levels by simply omitting dichloromethane from the coating solution and using another coating solution in its place. Both methods accomplish the same task, i.e., minimizing dichloromethane levels in coated particles. In fact, Lynenskjold *et al.* explicitly

suggest that while dichloromethane may be used as a solvent, it is generally **not** preferred (page 5, [0058]).

Applicant's argument that the Ishibishi reference discloses the use of dichloromethane and carbon tetrachloride as suitable solvents, which are "specifically excluded from the presently pending claims" is likewise unimpressive. As a first matter, the claims do not exclude carbon tetrachloride. Secondly, Applicant's argument does not take into account the full teachings of Ishibishi. While it is true that Ishibishi discloses that dichloromethane and carbon tetrachloride are suitable solvents, the reference broadly discloses that there are no particular restrictions on the solvent of the coating solution provided that it dissolves both the hydrophobic organic compound and water-soluble polymer. Ishibishi teaches, in addition to halogenated hydrocarbons such as dichloromethane and carbon tetrachloride, alcohols such as methanol, ethanol, and butanol, and ketones such as acetone (page 6, [0057]). Particularly preferred solvents are alcohols such as ethanol (id. at [0059]). Also note Comparative Example 1, wherein drug is dissolved in hydroxypropylcellulose (water-soluble polymer) and ethanol.

Applicant's argument that Lynenskjold et al. do not teach or suggest the combination of water and an organic solvent along with the water-soluble polymer is unimpressive because it is directed to the individual teachings of the reference without considering the reference as combined with Gilis, Ishibishi, and Nara. Lynenskjold teaches that the liquid to be spray-dried onto particle carriers may be prepared by dissolving the cellulosic binder in a heated solution of solvent (e.g, water), cooling to ambient temperature, and adding the "remaining components" (page 3, [0032]). Such remaining components include active drug substances, diluents and fillers, surfactants, etc. (page 2, [0027]). The reference further teaches that the active drug substance will generally be applied to the spray-dried pellets in the form of a solution or dispersion in a physiologically tolerable solvent or solvent mixture (page 4, [0050]) and that for coating spray-dried pellets, the use of aqueous solutions or dispersions is preferred but organic solvents such as ethanol or acetone may also be used. Lynenskjold explicitly teaches that chlorinated hydrocarbons such as methylene chloride are generally not preferred.

Applicant's acknowledge that Nara teaches a drug core coated with a coating composition comprising a water-insoluble substance, a swellable polymer, and optionally, hydrophilic substances dissolved or dispersed in a solvent, which solvent can be water, an

organic solvent, or mixtures thereof, but argue that the solvent system of Nara does not include a water-insoluble azole antifungal agent or any other agent. This argument is not persuasive because, again, Applicant's argument is directed to the individual teachings of the reference without considering the reference as combined with Gilis, Ishibishi, and Lynenskjold. Nara is simply provided as evidence that it was known in the art that solvents for coating solutions may be water, an organic solvent, or mixtures thereof (col. 6, lines 34-35), that the organic solvent may be any organic solvent capable of dissolving a water-insoluble substance, such as ethanol or acetone as recited in the instant claims (col. 6, lines 38-46), and that water and its mixture with an organic solvent are "preferably used as solvent of coating composition" (col. 6, lines 47-48). The fact that the solvent system discussed in Nara does not include water-insoluble azole antifungal agent or any other agent does not teach away from using this solvent system to coat inert particles with an active agent, as suggested and motivated by combined prior art.

Applicant's argument it would have been "unexpected" for a person having ordinary skill in the art to use water an organic solvent to process a water-insoluble drug is unimpressive in view of the combined teachings of the cited prior art. It is a proven scientific fact that water and acetone or alcohols such as ethanol and fully miscible. It is also a proven scientific fact that acetone is a "universal solvent" capable of dissolving both water-soluble and water-insoluble organic agents. As such, it would not be unexpected for a solution comprising water and ethanol and/or acetone to dissolve a water-insoluble antifungal agent. Further, optimization of a coating solution for applying a drug to an inert particle is more than routine in the art of drug formulation as evidenced by the cited prior art, which teaches that suitable solvent systems can comprise water, alcohols, ketones such as acetone, and/or chlorinated hydrocarbons. However, the cited prior art also teaches that the content of dichloromethane should be minimized (Gilis) and even goes so far as to state that chlorinated hydrocarbons are not preferred solvents (Lynenskjold).

Applicants argue that the Examiner has established no motivation to combine the cited references. In support of this argument, Applicants cite MPEP 2143.01, which states that the proposed modification cannot render the prior art unsatisfactory for its intended purpose. Applicant's argument that there is no motivation to combine the cited references is not persuasive because the cited prior art is drawn to coating bead cores with coating solutions comprising active agents, binders, solvents, excipients, etc. The closest prior art to Applicant's

claimed process is Gilis, who teaches that same process claimed by Applicants, differing only in the solvent used to coat the bead cores. Whereas Gilis discloses a solvent of dichloromethane and ethanol, Applicant's claim a solvent system comprising water and alcohol, acetone, or mixtures thereof. Ishibishi discloses using a solvent system capable of dissolving both the hydrophobic organic compound and water-soluble polymer (page 6, ¶ [0057]). Suitable solvents include alcohols such as ethanol as well as ketones such as acetone (*id.*). The reference thus teaches that ethanol and acetone are suitable solvents for applying a coating solution to a core particle. Applicant's argue that one skilled in the art would not substitute the solvent system of Lynenskjold or Nara containing water with that of Gilis or Ishibishi. This argument is unimpressive because Applicants have presented no factual evidence that modifying the solvent system of Gilis or Nara by addition of water as a co-solvent renders the prior art unsatisfactory for its intended purpose. The purpose of a solvent system for coating a bead core is to dissolve the constituents being applied to the bead core. Applicant's discovery that a solvent system of water and alcohol and/or acetone is capable of such is not patentable over the cited prior art, which suggests that solvents containing water, alcohols, ketones, and/or chlorinated hydrocarbons are suitable for coating bead cores. Further, one skilled in the art would recognize the benefits of reducing or eliminating chlorinated hydrocarbons from pharmaceutical preparations as these hydrocarbons are toxic. In fact, Gilis explicitly teaches that dichloromethane and methanol are both Class 2 solvents whose presence in pharmaceutical products should be limited (page 2, lines 28-30) and further teaches that residual solvent levels in coated pellets should be within limits set by the ICH, that is, the concentration of dichloromethane should be less than 600 ppm, most preferably less than 250 ppm (page 4, lines 24-32). Clearly, one skilled in the art would recognize that using a solvent system that does not contain dichloromethane would result in the desired concentration of dichloromethane of less than 250 ppm.

Applicant's argue that the process of the claimed invention provides particles unexpectdly superior with regard to solubility at pH 5.0, resulting in enhanced bioavailability of the active ingredient. In support of this argument, Applicants direct the Examiner to the itraconazole particles prepared according to parent application 09/933,032 (now USP No. 6,663,897) compared to commercially available SPORANOX particles prepared according to

USP No. 5,633,015. The Examiner has considered the comparison data presented by Applicants but is not persuaded that an unexpected result commensurate in scope with the claims has been demonstrated. The Examiner further submits that the SPORANOX particles prepared according to USP No. 5,633,015 do not allow for a direct comparison with the intraconazole particles prepared according to USP No. 6,663,897. As discussed above, the difference between Gilis et al. and the present claims is the solvent used in preparing coated particles. Whereas Gilis et al. use methylene chloride and ethanol, Applicants claim a solvent comprising water and alcohol and/or acetone. The itraconazole particles prepared according to USP No. 6,663,897 contain the following components:

1) Microcrystalline Cellulose Spheres --- 36.28%
2) Micronized Itraconazole --- 18.86%
3) HPMC --- 42.45%
4) Titanium Dioxide USP --- 0.85%
5) Hydrochloric Acid 37% --- 1.56%

The comparison itraconazole particles prepared according to USP 5,633,015 contain the following components:

1) Sugar Spheres --- 43.4%
2) Itraconazole --- 22.6%
3) HPMC --- 33.9%

It is readily apparent that not only are the particles prepared according to '015 prepared using a different solvent system, they also contain more core particles, more itraconazole, and less HPMC. Further, the itraconazole particles prepared according to '897 additionally contain titanium dioxide and hydrochloric acid, components not present in the particles of '015. As such, it is not clear how one can know that the increased dissolution observed at pH 5.0 for the particles prepared according to '897 is due to the solvent used to coat the core particles, as asserted by Applicants, and not to the lower amounts of core spheres and itraconazole and/or higher amounts of HPMC and/or the presence of titanium dioxide and hydrochloric acid. Further still, the particles prepared according to '015 are additionally coated with a seal-coating comprising polyethylene glycol 20000, a coating not applied to the itraconazole particles prepared according to Applicant's invention. In view of the above analysis, Applicant's

argument that particles coated according to the claimed invention exhibit unexpectedly superior dissolution at pH 5.0 is unimpressive. The instant claims place no restriction on amounts or type of core particles, amounts of antifungal agent, or amounts or type of water-soluble polymer and further do not recite the inclusion of titanium dioxide or hydrochloric acid. As such, Applicants have not compared particles commensurate in scope with the claims with the closest prior art particles. For such a comparison, Applicants would need to compare dissolution of particles according to '015 prepared by using a solvent system of the instant claims with particles according to '015 prepared by using other solvent systems not encompassed by the claims. The cited prior art teaches that there are numerous solvents and combinations of solvents that are useful in coating particles with active agents. The primary reference, Gilis, provides one skilled in the art with the needed motivation to look for solvents or combinations of solvents that do not contain dichloromethane, stating that dichloromethane and methanol are both Class 2 solvents whose presence in pharmaceutical products should be limited (page 2, lines 28-30) and further stating that residual solvent levels in coated pellets should be within limits set by the ICH, that is, the concentration of dichloromethane should be less than 600 ppm, most preferably less than 250 ppm (page 4, lines 24-32). Clearly, using a solvent system that does not contain dichloromethane would best achieve a dichloromethane solvent level in coated pellets of less than 250 ppm.

Claim 7 remains rejected under 35 U.S.C. 103(a) as being unpatentable over **Gilis *et al.*** (WO 00/03697; Published Jan. 27, 2000), **Ishibashi *et al.*** (U.S. Patent Application Publication No. US 2003/0012815 A1; Published Jan. 16, 2003; Filed Jan. 26, 2001), **Lynenskjold *et al.*** (US 2003/0211168 A1; Published Nov. 13, 2003; Filed Feb. 19, 2001), and ***Nara et al.*** (USP No. 6,245,351 B1; Issued Jun. 12, 2001; Filed Mar. 4, 1997) as applied to claims 1-6, 15-16, 18-20, 22-23, and 42 above, and further in view of **Vladyka *et al.*** (USP No. 6,497,905 B1; Issued Dec. 24, 2002; Filed Mar. 20, 2000), each already of record, for the reasons set forth at page 12 of the previous Office Action dated 12/4/2008, of which said reasons are herein incorporated by reference.

Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* teach as applied *supra* and are here applied to claim 7 in the same manner. The references do not teach the amorphous form of an azole antifungal agent as recited in claim 7.

However, Vladyka *et al.* teach that members of the class of azole antifungal agents such as ketoconazole and itraconazole have very low solubility in aqueous media and will benefit from the method of conversion to the amorphous state (col. 5, lines 36-43).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to provide the claimed azole antifungal agent in the amorphous state because Vladyka et al. teach that these agents having low aqueous solubility will benefit from providing them in their amorphous state. The skilled artisan would reasonably expect that an azole antifungal agent in its amorphous state will exhibit increased solubility (Vladyka et al., col. 5, lines 20-25) in the aqueous coating solutions as motivated and suggested by Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* as discussed *supra*.

Response to Applicant's Arguments

Applicants argue that the cited references do not establish a prima facie case of obviousness against the presently pending claims. With regard to the teachings of Gilis et al., Ishibashi et al., Lynenskjold et al., and Nara et al., the Examiner's discussion above is hereby incorporated by reference. Applicant's argue that Vladyka et al., while teaching a solid solution of an azole comound in an amorphous state dissolved in a molten solution of hydrophobic vehicle, a stablizing agent, a disintegrant, and optionally a binder, teaches that this composition is formulated in a different method than that presently claimed. This argument is not persuasive because Vladyka is not relied upon by the Examiner for teaching the claimed process, but rather that the teaching that members of the class of azole antifungal agents such as ketoconazole and itraconazole have very low solubility in aqueous media and will benefit from the method of conversion to the amorphous state. As such, utilizing a water-insoluble azole antifungal agent in its amorphous state in the preparation of the coated particles suggested and motivated by the cited prior art would have been prima facie obvious to one of ordinary skill in the art.

Claim 17 remains rejected under 35 U.S.C. 103(a) as being unpatentable over **Gilis *et al.*** (WO 00/03697; Published Jan. 27, 2000), **Ishibashi *et al.*** (U.S. Patent Application Publication No. US 2003/0012815 A1; Published Jan. 16, 2003; Filed Jan. 26, 2001), **Lynenskjold *et al.*** (US 2003/0211168 A1; Published Nov. 13, 2003; Filed Feb. 19, 2001), and **Nara *et al.*** (USP No. 6,245,351 B1; Issued Jun. 12, 2001; Filed Mar. 4, 1997) as applied to claims 1-6, 15-16, 18-20, 22-23, and 42 above, and further in view of **Martindale: The Complete Drug Reference** (Pharmaceutical Press, London, 2002, pages 1344-1349), each already of record, for the reasons set forth at page 13 of the previous Office Action dated 12/4/2008, of which said reasons are herein incorporated by reference.

Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* teach as applied *supra* and are here applied to claim 17 in the same manner. The references do not teach the specific surfactants as recited in claim 17.

However, Martindale teaches that surfactants are compounds that can reduce the interfacial tension between two immiscible phases (page 1344), specifically teaching that polysorbates (20, 40, 60, and 80), polyoxyl castor oils, poloxamers, and sorbitan esters (*e.g.*, sorbitan laureate, sorbitan palmitate, and sorbitan stearate) are suitable for use as surfactants in the manufacture of pharmaceuticals (pages 1346-1349).

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use any known surfactant, such as those taught by Martindale, in the manufacture of azole antifungal-coated particles. Gilis *et al.* teach that surfactants can be incorporated in pharmaceutical preparations comprising azole antifungal agents. As such, the skilled artisan would have been imbued with at least a reasonable expectation that the surfactants taught in Martindale would be amiable for use in the coating methods suggested and motivated by the cited references.

Response to Applicant's Arguments

Applicants argue that the cited references do not establish a prima facie case of obviousness against the presently pending claims. With regard to the teachings of Gilis et al., Ishibashi et al., Lynenskjold et al., and Nara et al., the Examiner's discussion above is hereby incorporated by reference. Applicants argue that none of Gilis et al., Ishibashi et al.,

Lynenskjold et al., and Nara et al. teach the surfactants recited in claim 17. The Examiner is aware of this fact as he explicitly stated such in the above rejection: "[T]he references do not teach the specific surfactants as recited in claim 17". While acknowledging that the Martindale reference recites surfactants that are suitable for use in pharmaceuticals, Applicants argue that Martindale fails to cure the "other deficiencies" of Gilis et al., Ishibashi et al., Lynenskjold et al., and Nara et al. A lengthy response to Applicant's arguments against Gilis et al., Ishibashi et al., Lynenskjold et al., and Nara et al. is provided above and is herein incorporated by reference.

Double Patenting – New Ground of Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7, 15-20, 22-23, and 42 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,663,897. Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently examined application claims are anticipated by or would have been obvious over the methods of manufacturing an itraconazole oral dosage form that is substantially free of residual methylene chloride as recited in the '897 patent claims. While the claims of the

'897 patent recite a working solution additionally comprising a strong acid, the instant claims do not exclude the presence of a strong acid in the working solution. Furthermore, while the claims of the '897 patent are limited to particles comprising itraconazole, it would have been obvious to one skilled in the art at the time the invention was made that the methods of the '897 patent would also be effective in forming oral dosage forms comprising other water-insoluble antifungal agents such as ketoconazole as recited in instant claim 42.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614